Inhibition of invasive pancreatic cancer: restoring cell apoptosis by activating mitochondrial p53.

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Public Summary:
Pancreatic ductal adenocarcinoma (PDAC), constitutes >90% of pancreatic cancers (PC) and is one of the most aggressive human tumors. Standard chemotherapies for PDAC (e.g., gemcitabine, FOLFIRINOX, etc.) has proven to be largely ineffective. Herein, we report a novel molecule (i.e., compound 1) that potently inhibits proliferation and induces apoptosis of PDAC cells. As we observed in other cancer types (i.e., colorectal, breast cancer), the effect of 1 against PDAC cells is also related to microtubule destabilization and DNA damage checkpoint activation. However, in PDAC cells, the inhibitory effect of 1 was mainly controlled by mitochondrial p53-dependent apoptosis. Compound 1 worked with cells of different p53 mutant status and affected p53 activation/phosphorylation not simply by stabilizing p53 protein but through antagonizing anti-apoptotic effects of Bcl-xL and restoring p53 to activate mitochondrial-apoptotic pathways (i.e., cytochrome c release, caspase activation and PARP cleavage). Compound 1 was more efficient than a typical PDAC combination therapy (i.e., gemcitabine with paclitaxel) and showed synergism in inhibiting PDAC cell proliferation with gemcitabine (or gemcitabine with paclitaxel). This synergism varied between different types of PDAC cells and was partially controlled by the phosphorylation of p53 on Serine15 (phospho-Ser15-p53). In vivo studies in an orthotopic syngeneic murine model showed that 1 (20 mg/kg/day, 28 days, i.p.) inhibited tumor growth by 65% compared to vehicle-treated mice. No apparent acute or chronic toxicity was observed. Thus, compound 1 utilizes a distinct mechanism of action to inhibit PC growth in vitro and in vivo and is a novel anti-PDAC compound.

Scientific Abstract:
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